1646 AF #15 DMJ 6-29-01

BEFORE THE BOARD OF APPEALS AND INTERFERENCES
IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of: Lustig et al.	Group Art Unit: 1646
Serial No. 09/163,713	Examiner: Pak, M.
Filed: September 30, 1998	Attorney Docket No. T97-012-1
For: *Nuclear Hormone Receptor Drug Screens*	CERTIFICATE OF MAILING I hereby certify that this corr is being deposited with the US Postal Service as First Class Mail in an envelope addressed to the Comm. of Patents, Washington, D.C. 20231 on June 20, 2000. Signed _____ Richard Osman

BRIEF ON APPEAL

The Assistant Commissioner of Patents
Washington, D.C. 20231

Dear Commissioner:

This is an appeal from the 1/17/01 final rejection of claims 32-61.

REAL PARTY IN INTEREST

The real party in interest is Tularik Inc., the assignee of this patent application.

RELATED APPEALS AND INTERFERENCES

Appellants have noticed appeal and will be filing an appeal brief in the parent of this application, Serial No. 08/975,614; Appellants are unaware of any other related appeals or interferences.

STATUS OF THE CLAIMS

Claims 32-61 are pending and subject to this appeal.

STATUS OF THE AMENDMENTS

All Amendments are believed to be properly before the Board.

SUMMARY OF THE INVENTION

Nuclear hormone receptors comprise a large, well-defined family of ligand-activated transcription factors which modify the expression of target genes by binding to specific cis-acting sequences. Family members include both orphan receptors and receptors for a wide variety of clinically significant ligands including steroids, vitamin D, thyroid hormones, retinoic acid, etc. Ligand binding is believed to induce a conformational change in the receptors and promote their association with transcriptional coactivators, which are a diverse group of large nuclear proteins, which may share a signature sequence motif. The resulting complex then binds high affinity sites in chromatin and modulates gene transcription. Specification, p.1, lines 15-25.

The classic approach to identifying agonists or antagonists of nuclear hormone receptors is the ligand displacement assay, where the displacement of radiolabeled ligand by candidate agents is detected. An alternative approach is a cell-based transcription assay for expression of a reporter of nuclear hormone receptor activation. More recently, a gel-based coactivator dependent receptor ligand assay has been used to identify ligands of peroxisome proliferator-activated receptors (PPARs), which are nuclear hormone receptors activated by a variety of compounds including hypolipidemic drugs. Unfortunately, these various assays suffer from a number of limitations including a required known ligand and time, labor and resource intensive cell-based and gel-based methods, respectively. Specification, p.1, line 26 - p.2, line 4.

Our invention provides methods for efficient screening of modulators of nuclear hormone receptor function, without the use of cell- or gel-based steps. The methods are amenable to automated, cost-effective high throughput screening of chemical libraries for bioactive compounds. Specification, p.2, lines 6-9.

Pursuant to our only independent claim, the invention provides an in vitro assay method for modulators of a nuclear hormone receptor binding function, the method comprising the steps of (a) forming an in vitro mixture comprising a first nuclear hormone receptor, a peptide sensor and a candidate agent, but not a natural coactivator protein of the first receptor, wherein the sensor consists of a peptide comprising the sequence $L_1X_1X_2L_2L_3$ (SEQ ID NO:18) covalently coupled to a detectable label, wherein L_1-L_3 are independently selected from hydrophobic amino acids and X_1-X_2 are independently selected from any amino acid and wherein the peptide

provides direct, in vitro ligand-dependent binding to the first receptor and is 24 or fewer residues in length; (b) measuring an agent-biased binding of the sensor to the first receptor by detecting immobilized first receptor-sensor complexes; and (c) comparing the agent-biased binding with a corresponding unbiased binding of the sensor to the first receptor; wherein a difference between the biased and unbiased bindings indicates that the agent modulates a binding function of the first receptor. Specification, p.2, lines 10-17; claim 32.

ISSUES

I. WHETHER CLAIMS 32-53 and 56-61 ARE PATENTABLE UNDER 35USC112, first paragraph (written description).

II. WHETHER CLAIMS 32-61 ARE PATENTABLE UNDER 35USC112, first paragraph (enablement).

GROUPING OF THE CLAIMS

For Issue I, claims 32-53 and 56-61 shall be considered together as a group.

For Issue II, claims 32-53 and 56-61 shall be considered together as a group; and claims 54-55 shall be considered as a separate group.

ARGUMENT

I. CLAIMS 32-53 and 56-61 ARE PATENTABLE UNDER 35USC112, first paragraph (written description).

Claims 32-53 and 56-61 comply with the written description requirement of 35USC112, first paragraph. The rejection is premised on the supposition that our Specification describes only leucine for the recited L_1-L_3. In fact, our Specification clearly describes L_1-L_3 as independently selected from hydrophobic amino acids, preferably leucine or isoleucine, more preferably leucine. See Specification, p.4, lines 27-30. Furthermore, the same exact limitation on L_1-L_3 was present in original claim 6. Our written description is not limited to an expressly characterized particularly preferred embodiment.[1]

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[1] The holding of the cited *UC v. Lilly* (43USPQ2d1398) hardly supports this rejection. In *Lilly*, the applicant claimed a genus of every "vertebrate cDNA encoding insulin", while only

II. CLAIMS 32-61 ARE PATENTABLE UNDER 35USC112, first paragraph (enablement).

Our claims 32-61 comply with the enablement requirement of 35USC112, first paragraph. The enablement issue is whether our Specification enables one of ordinary skill in the art to practice the invention without undue experimentation.

The first stated rejection, applied to claims 54-55, is premised on the suppositions that the claims encompass a sensor peptide comprising SEQ ID NO:11, that such a peptide does not work, and that the claims therefore require undue experimentation to practice. In fact, the claimed methods require a peptide that "works" – i.e. which provides direct, in vitro ligand-dependent binding to a nuclear hormone receptor. Hence, the claims do not encompass the supposed inoperable embodiments. Second, the Specification does not teach that use of a peptide comprising SEQ ID NO:11 is inoperable: the cited *exemplary* binding data of our Table 2 is limited to particular nuclear hormone receptors in a particular fluorescent polarization assay. Every combinatorially possible peptide will not and need not work with every receptor under every condition – in fact, assay specificity would be compromised if that were the case. Third, the claims would be compliant with the enablement requirement even if there were inoperable embodiments.[2] And fourth, ascertaining the suitability of any given candidate peptide species is well within the bounds of empirical experimentation permitted by the enablement requirement of

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disclosing the corresponding rat cDNA. Isolating other members of the claimed cDNA genus would involve de novo cloning from each species, as UC's claim required sequences which are, or are the same as, sequences isolated from a given vertebrate species. Hence, UC's description relied upon the practitioner going out and cloning de novo novel sequences from alternative species. Under these facts, the Federal Circuit determined that the rat cDNA did not reasonably convey possession of the genus of every vertebrate cDNA. In our facts, there is no claim to cDNA, nor any requirement that the practitioner isolate anything from nature. Those skilled in the art (and those with access to an introductory biology or biochemistry text) know exactly what is a hydrophobic amino acid, as described and exemplified in our specification.

[2] "It is not a function of the claims to specifically exclude possible inoperative substances", *In re Dinh-Nguyen*, 181USPQ46,48(CCPA 1974); see also, *In re Wands* (8 USPQ2d 1400 (Fed Cir 1988), "Even if we were to accept the PTO's 2.8% success rate, we would not be required to reach a conclusion of undue experimentation"; see also, *Atlas Powder Co.*, 224USPQ409,414 (Fed Cir 1994); and, as noted above, the claims do not even encompass such conceptual inoperative embodiments.

35USC112, as defined by applicable Federal Circuit law; see *In re Wands* (8 USPQ2d 1400 (Fed Cir 1988). [3]

The second stated rejection, applied to claims 32-53 and 56-61, is premised on the same erroneous supposition as that of the written description rejection: that our Specification describes only leucine for the recited L_1-L_3. In fact, our Specification clearly teaches that L_1-L_3 are independently selected from hydrophobic amino acids, preferably leucine or isoleucine, more preferably leucine. See Specification, p.4, lines 27-30. As noted above, the claimed sensors (and respective methods) require a peptide which provides direct, in vitro ligand-dependent binding to a nuclear hormone receptor. The Specification exemplifies the sensors and methods with a wide variety of suitable exemplary peptides with several receptors. Specification, p.5, line 24 - p.7, line 9. For additional sensor peptides, the Specification teaches that panels of predetermined or randomized candidate sensors are readily screened for differential binding, as exemplified in Figures 2 and 3 for two exemplary receptor/ligand pairs. Specification, p.5, lines 14-16. The assay is a rapid, high-throughput, simple in vitro binding assay, well within the bounds of empirical experimentation permitted by the enablement requirement of 35USC112 as defined by applicable Federal Circuit law, see e.g. *In re Wands* (supra).

The empirical experimentation necessary to practice alternative embodiments of our invention is trivial compared with that permitted under *Wands*. Substituting and testing an

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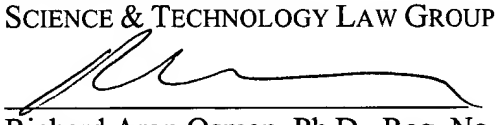
[3] In *Wands*, the Federal Circuit held that making and screening monoclonal antibodies, even back in 1980, did not constitute undue experimentation. Consider what is *not* undue experimentation: first, immunize, bleed and immunoassay panels of mice, wherein the immunoassay itself is a binding affinity assay; then, after immunizing and confirming the presence of requisite specific antibodies, practitioners of Wand's invention are faced with the daunting and unpredictable tasks of surgically removing the animal's spleen; separating lymphocytes therefrom; mixing the lymphocytes with myeloma cells; treating the mixture to cause a few of the lymphocytes to fuse with a few myeloma cells; isolating from the enormous number of cells in the mixture hybridoma cells that secrete the desired antibody through a series of screening procedures. The entire post-immunization process through serial cloning takes months. The technical feats involved include aseptic surgery, cell fusions, tissue culture with transformed cells which require special health and environmental safety measures, dilution cloning, usually into a bed of immature thymocytes which again requires further aseptic surgery, radiolabel or enzyme-linked immunoassays of secreted antibody, etc. In fact, the vast majority (>97%) of Wand's efforts to produce the claimed antibodies failed.

alternative hydrophobic amino acid for leucine in the finely taught, simple binding assays does not approach the experimentation required by Wands. Our Specification provides more than sufficient teaching to enable one of ordinary skill in this art to practice the claimed invention without undue experimentation. As the 35USC112-compliant experimentation required to generate and screen monoclonal antibodies per *Wands* is vastly more extensive and unpredictable than that required here, our claims are in compliance with the enablement requirement of 35USC112.

Applicants respectfully request reversal of the pending Final Action by the Board of Appeals.

Applicants petition for any necessary extension of time (small entity) pursuant to 37 CFR 1.136(a). The Commissioner is hereby authorized to charge any fees or credit any overcharges associated with this communication to our Deposit Account No. 19-0750 (order no. T97-012-1).

Respectfully submitted,
SCIENCE & TECHNOLOGY LAW GROUP



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CLAIMS ON APPEAL

32. An in vitro assay method for modulators of a nuclear hormone receptor binding function, comprising steps:

forming an in vitro mixture comprising a first nuclear hormone receptor, a peptide sensor and a candidate agent, but not a natural coactivator protein of the first receptor, wherein the sensor consists of a peptide comprising the sequence $L_1X_1X_2L_2L_3$ (SEQ ID NO:18) covalently coupled to a detectable label, wherein L_1-L_3 are independently selected from hydrophobic amino acids and X_1-X_2 are independently selected from any amino acid and wherein the peptide provides direct, in vitro ligand-dependent binding to the first receptor and is 24 or fewer residues in length;

measuring an agent-biased binding of the sensor to the first receptor by detecting immobilized first receptor-sensor complexes;

comparing the agent-biased binding with a corresponding unbiased binding of the sensor to the first receptor;

wherein a difference between the biased and unbiased bindings indicates that the agent modulates a binding function of the first receptor.

33. A method according to claim 32, wherein the measuring step comprises detecting the first receptor of immobilized first receptor-sensor complexes.

34. A method according to claim 32, wherein the measuring step, the first receptor is immobilized through the sensor.

35. A method according to claim 32, wherein the measuring step, the first receptor is immobilized through the sensor and the sensor is immobilized through the label.

36. A method according to claim 32, wherein the measuring step, the first receptor is immobilized through the sensor, and the sensor is immobilized through the label by a second receptor.

37. A method according to claim 32, wherein the measuring step, the first receptor is immobilized through the sensor, and the sensor is immobilized through the label by a second receptor and wherein the measuring step comprises detecting the immobilized first receptor.

38. A method according to claim 32, wherein the measuring step, the first receptor is immobilized through the sensor, and the sensor is immobilized through the label by a second receptor and wherein the measuring step comprises detecting the immobilized first receptor with a third receptor.

39. A method according to claim 32, wherein the sensor comprises an epitope label, wherein the measuring step, the first receptor is immobilized through the sensor and the sensor is immobilized through the label by a second receptor comprising an immobilized epitope label-specific antibody moiety.

40. A method according to claim 32, wherein the sensor comprises a biotin label and wherein the measuring step, the first receptor is immobilized through the sensor and the sensor is immobilized through the label by a second receptor comprising an immobilized avidin moiety.

41. A method according to claim 32, wherein the measuring step, the sensor is immobilized through the first receptor.

42. A method according to claim 32, wherein the measuring step, the sensor is immobilized through the first receptor and the first receptor is immobilized through a second receptor.

43. A method according to claim 32, wherein the measuring step, the sensor is immobilized through the first receptor and the first receptor is immobilized through a second receptor and wherein the measuring step comprises detecting the immobilized sensor.

44. A method according to claim 32, wherein the measuring step, the sensor is immobilized through the first receptor and the first receptor is immobilized through a second receptor and wherein the measuring step comprises detecting the immobilized sensor with a third receptor.

45. A method according to claim 32, wherein the measuring step, the sensor is immobilized through the first receptor and the first receptor is immobilized through a second receptor comprising a receptor specific antibody.

46. A method according to claim 32, wherein the first receptor comprises the ligand binding domain of PPARγ, Cyp7PBP(LRH-1), NURR1, RZRβ, RORα, NOR-1, Rev-ErbAβ, Tlx, NGFI-

Bβ, HZF-2α, COUP-TFα, β, γ, Nur77, LXRα, COR, Rev-ErbAα, HNF4α, TOR, MB67α, SHP, FXR, SF-1, LXRβ, GCNF, TR2-11α,β, TR4, ERRα,β and DAX-1

47. A method according to claim 32, wherein the agent effects an increase in binding of the sensor to the first receptor.

48. A method according to claim 32, wherein the sensor is at a concentration of less than about 10 nM.

49. A method according to claim 32, wherein the first receptor, peptide and agent are in solution.

50. A method according to claim 32, wherein the peptide comprises a fluorescent label and the measuring step comprises detecting fluorescence polarization of the label.

51. A method according to claim 32, wherein the mixture further comprises a ligand of the first receptor.

52. A method according to claim 32, wherein the peptide is 12 or fewer residues in length.

53. A method according to claim 32, wherein the peptide comprises an amphipathic alpha helix.

54. A method according to claim 32, wherein the peptide comprises a sequence selected from the group consisting of: KLVQLLTTT (SEQ ID NO:1), ILHRLLQE (SEQ ID NO:2), LLRYLLDK (SEQ ID NO:3), LLRYLLD (SEQ ID NO:4), LRYLLD (SEQ ID NO:5), LLRYLL (SEQ ID NO:6), LRYLL (SEQ ID NO:7), LLRYLLDKD (SEQ ID NO:8), QLLRYLLDKD (SEQ ID NO:9), HQLLRYLLDKD (SEQ ID NO:10), PQAQQKSLLQQLLT (SEQ ID NO:11), LLQQLLTE (SEQ ID NO:12), VTLLQLLLG (SEQ ID NO:13), ILRKLLQE (SEQ ID NO:14, ILKRLLQE (SEQ ID NO:15), ILRRLLQE (SEQ ID NO:16) and ILKKLLQE (SEQ ID NO:17).

55. A method according to claim 32, wherein the peptide consists of a sequence selected from the group consisting of: KLVQLLTTT (SEQ ID NO:1), ILHRLLQE (SEQ ID NO:2), LLRYLLDK (SEQ ID NO:3), LLRYLLD (SEQ ID NO:4), LRYLLD (SEQ ID NO:5), LLRYLL (SEQ ID NO:6), LRYLL (SEQ ID NO:7), LLRYLLDKD (SEQ ID NO:8), QLLRYLLDKD (SEQ ID NO:9), HQLLRYLLDKD (SEQ ID NO:10), PQAQQKSLLQQLLT (SEQ ID NO:11),

LLQQLLTE (SEQ ID NO:12), VTLLQLLLG (SEQ ID NO:13), ILRKLLQE (SEQ ID NO:14, ILKRLLQE (SEQ ID NO:15), ILRRLLQE (SEQ ID NO:16) and ILKKLLQE (SEQ ID NO:17).

56. A method according to claim 32, wherein the label provides for indirect detection of the sensor.

57. A method according to claim 32, wherein the label provides for indirect detection of the sensor, wherein the label is an epitope tag.

58. A method according to claim 32, wherein the label provides for direct detection of the sensor.

59. A method according to claim 32, wherein the label provides for direct detection of the sensor, wherein the label is a luminescent label.

60. A method according to claim 32, wherein the label provides for direct detection of the sensor, wherein the label is a luminescent label, wherein the luminescent label is a fluorescent label.

61. A method according to claim 32, wherein the label provides for direct detection of the sensor, wherein the label is a luminescent label, wherein the luminescent label is a fluorescent label, wherein the fluorescent label is coupled to the N-terminus of the peptide.